Evidence for a slow water diffusion pool swelling during activation of human visual cortex

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Introduction

A transient decrease of the apparent diffusion coefficient (ADC) has been reported during activation of human visual cortex (1). This small effect has been tentatively ascribed to cell swelling, offering an exciting alternative to BOLD fMRI. Our aim was to check this hypothesis by investigating signal changes at different degrees of diffusion sensitization and by analyzing data using a simple 2-compartment water diffusion model of the brain cortex.

Materials & Methods

The study was performed on 6 volunteers using a 3T MRI scanner equipped with a 8-channel phased-array coil. To eliminate diffusion signal contamination by BOLD induced susceptibility effects (2) a twice refocused spin-echo EPI sequence sensitized to diffusion by an interleaved pair of bipolar gradient pulses was chosen (3). Acquisition parameters were: voxel size=3.8^{3}mm^3, GRAPPA encoding (g=2), TE=87ms/TR=1s. Visual stimulation was obtained from a flickering dartboard during 3 epochs of 20 (or 16) seconds separated by a 20 second interval. The acquisition was repeated with 4 b values in random order (b=600, 1200, 1800 and 2400 s/mm^2). A set of 18 diffusion-sensitized images was also acquired in a resting condition with b values ranging from 0 to 3400 s/mm^2 with 200 s/mm^2 increments for the diffusion compartment analysis. Activation maps were calculated individually for each subject from the b=2400 s/mm^2 diffusion-sensitized data set using SPM software and a volume of interest (VOI) centered on calcarine fissures was defined from the voxels classified as activated (0.001 threshold). This VOI was then used subsequently for analyzing all data. First, the VOI averaged signal from the 18 b values data set was plotted against b value and fitted to a 2-compartment model to estimate the volume fraction (f_i) and the diffusion coefficient (D_i) associated to the slow and fast diffusion pools (4): $S/S_0 = f_{slow} \exp(-b\, D_{slow}) + f_{fast} \exp(-b\, D_{fast})$ [1].

Second, the VOI averaged signal time course was extracted for each b value (600, 1200, 1800 and 2400 s/mm^2) and plotted. The signal from the resting and activated conditions were then pooled separately in order to estimate the signal change (dS/S) induced by activation at each b value. In a first approach S_0, D_{slow} and D_{fast} were set to remain constant during activation, so that, assuming small signal variations, the relative signal change could be modeled from Eq.(1) as:

$$dS/S = F_{slow}\, df_{slow} + F_{fast}\, df_{fast} \quad , \text{with } F_{i=fast,\,slow} = \exp(-bD_i) / [\, f_{slow} \exp(-bD_{slow}) + f_{fast} \exp(-bD_{fast})] \qquad [2]$$

where df_i is the change in volume fraction of the slow and fast diffusion pools resulting from activation. A least-square bilinear fitting algorithm was used to freely estimate the respective water volume changes, df_{slow} and df_{fast} (without a $f_{slow}+f_{fast,}=1$ constraint) from the signal changes observed for each b value using Eq.[2] and the VOI diffusion parameters for each subject. The observed and model signal changes, dS/S, were plotted against b values for each subject.

Results

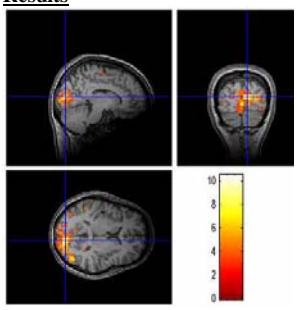

Fig.1: SPM activation map from a b=2400 s/mm^2 diffusion-sensitized data set showing areas of increased signal (decreased diffusion) in subject Na...

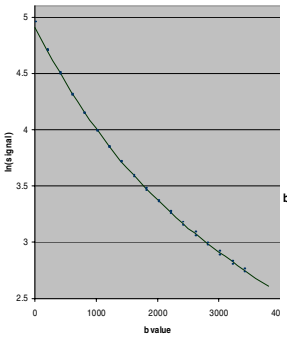

Fig.2: Plot of ln(S/So) in SPM VOI as a function of b value and adjusted model, showing biexponential decay.

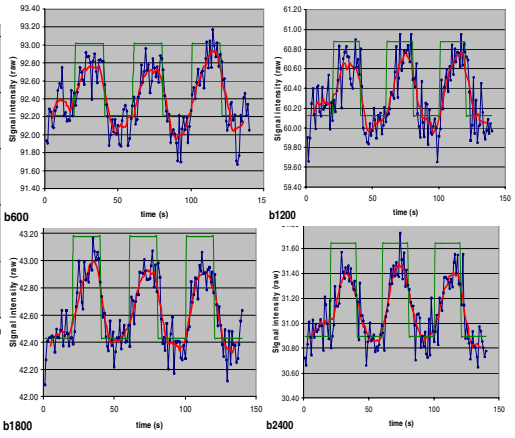

Fig.3: VOI signal time courses for each diffusion-sensitized data set for subject Na… (b=600, 1200, 1800 and 2400 s/mm^2).

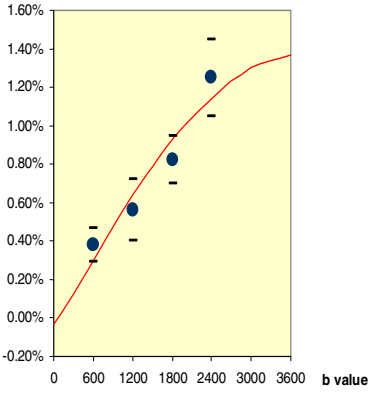

Fig.4: VOI plot of dS/S against b value for subject Na…(blue: data, red: adjusted model from Eq.[2]).

Results were remarkably consistent across our 6 subjects (Table 1). Activation of visual cortex was well defined (Fig.1). Diffusion attenuation curves clearly exhibited biexponential decay (Fig.2) and fitting with Eq.[1] gave results very consistent with literature (5). A diffusion-weighted signal increase was found for each b-value (Fig.3), but the signal change dS/S increased with b value (Fig.4). This increase with b value was very well modeled by a change of the volume fractions of the slow and fast diffusion pool (and not by a change in the pool diffusion coefficients, D_{slow} and D_{fast}, data not shown). Interestingly, the amount of volume increase of the slow diffusion pool (+0.56%) and that of the volume decrease of the fast diffusion pool (-0.44%) were not statistically different, suggesting that a transfer of water occurs from the fast to the slow diffusion pool during activation resulting in a 1.69±0.27% overall relative swelling of the slow diffusion pool.

Subject	VOI size (voxels)	f_{slow}	df_{slow}			swelling	df_{fast}		
TA..	72	35.2%	0.50%	±	0.06%	1.41%	-0.35%	±	0.23%
NA..	127	34.1%	0.65%	±	0.05%	1.90%	-0.40%	±	0.22%
HI..	127	34.0%	0.49%	±	0.06%	1.44%	-0.52%	±	0.23%
BA..	90	29.9%	0.62%	±	0.10%	2.06%	-0.64%	±	0.33%
YA..	148	32.2%	0.50%	±	0.06%	1.55%	-0.34%	±	0.30%
CH..	175	33.1%	0.60%	±	0.10%	1.82%	-0.37%	±	0.36%
Average	**123**	**33.1%**	**0.56%**	±	**0.07%**	**1.69± 0.27%**	**-0.44%**	±	**0.12%**

Table 1: Results from all subjects. Slow diffusion pool swelling amount was calculated as df_{slow}/f_{slow}

Discussion and conclusion

The decreased ADC observed in (1) resulted from a single compartment model. This study suggests that this apparent diffusion decrease might result from the shift of water from a fast to a slow diffusion compartment. Several groups have shown that brain water diffusion could be accurately described using a biexponential function modeling a fast and a slow diffusion pool in slow exchange. Unfortunately the nature of those pools remains a subject of investigation, as their volumes do not match respectively the extra- and intracellular volume fractions, as initially thought. Although the origin of the pools is unclear our data strongly support that a swelling of the slow diffusion water pool occurs during cortical activation, at the expense of the fast diffusion pool. Further studies will be, of course, necessary to assign this slow diffusion pool to cortical cells and to explain the origin of the swelling through the flux of ion/water. However, diffusion-sensitized MRI, especially at high b-value and high Bo, appears as a promising approach for fMRI, as it might provide quantitative access to a direct physiological surrogate of cortical activation.

References

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